In the Claims

Please cancel Claim 67. Amend Claims 44-45 and 50-51 as follows:

44. (Four Times Amended) A method of immunizing a mammal against an immunodeficiency virus of interest selected from the group consisting of: simian immunodeficiency virus and human immunodeficiency virus, said method comprising administering to the mammal a DNA transcription unit comprising DNA encoding an antigen of [the] said immunodeficiency virus of interest operatively linked to DNA which is a promoter region, in a physiologically acceptable carrier, wherein the DNA transcription unit is expressed in cells of the vertebrate, whereby the mammal is protected from disease caused by [the] said immunodeficiency virus of interest.

45. (Amended) The method of Claim 44, wherein the DNA transcription unit is administered in combination with one or more additional DNA transcription units, each comprising DNA encoding a different antigen of [the] said immunodeficiency virus of interest operatively linked to a promoter region.

50. (Amended) The method of Claim 44, wherein the immunodeficiency virus of interest is simian immunodeficiency virus.

51. (Amended) The method of Claim 44, wherein the immunodeficiency virus of interest is human immunodeficiency virus.

REMARKS

Claim 67 has been canceled. Claim 44 has been amended to specify that the immunodeficiency virus is simian immunodeficiency virus (SIV) or human immunodeficiency virus (HIV). Support for this amendment is found throughout the specification, and particularly,

for example, at page 9, lines 3-4, and the Examples. No new matter has been added. Claims 45, 50 and 51 have been amended to reflect the language of amended Claim 44.

Claims 44-46, 50-51, 62-64, 68-70, 74 and 78-89 are pending. The remainder of these Remarks is set forth under appropriate headings for the convenience of the Examiner.

Pending Claims

Methods Claims

Claims 44-46, 50, 51 and 89-89 are drawn to methods of immunizing a mammal against an immunodeficiency virus of interest, by administering a DNA transcription unit comprising DNA encoding an antigen of that immunodeficiency virus of interest operatively linked to DNA which is a promoter region, wherein the mammal is protected from disease caused by that immunodeficiency virus of interest. The immunodeficiency virus of interest is SIV or HIV, and the promoter can be of retroviral origin or not of retroviral origin. The DNA transcription unit can be administered by a variety of different routes of administration.

As described in the Specification at page 7, lines 5-8, "immunizing" as used in the claims refers to production of an immune response which protects, *partially or totally*, from the *manifestations of infection* (i.e., disease) caused by the infectious agent. Furthermore, immunizing can result in protection against infection, or infection to a lesser extent than would occur without immunization (page 7, lines 9-11). Thus, "immunizing" does not refer solely to protection against infection *per se* (although that is contemplated), but rather, refers also to generation of an immune response that *lessens or eliminates* manifestations of disease after infection with the infectious agent.

Construct Claims

Claims 62-64, 68-70, 74 and 78-80 are drawn to compositions comprising one or more specific DNA transcription units. The transcription units, described in detail in the Specification at page 45, line 16, *through* page 49, line 9 (HIV constructs) and page 53, line 11, through page 55, line 28 (SIV constructs). These constructs are useful, for example, in methods as described above.

Remaining Rejections

The Examiner set forth several remaining issues, including rejections under 35 U.S.C. 112, first paragraph. Each of the issues is addressed in the order in which they were raised in the Office Action.

Scope of Methods Claims

The Examiner stated that the method claims were not limited to SIV or HIV, but broadly encompassed any immunodeficiency virus. In order to facilitate prosecution of the application, the claims have been amended to specify that the immunodeficiency virus of interest is SIV or HIV.

The Examiner also stated that the method claims were not limited to constructs taught by Applicants. The constructs described in the Specification, and further described in the Declaration under 37 C.F.R. 1.132 of Dr. Harriet L. Robinson (the "Data Declaration") (and acknowledged in the Office Action as being the same as those described in the Specification), are representative of the types of constructs which are useful in the claimed methods. Applicants have described in detail how to prepare constructs (both SIV-related and HIV-related) (see Examples 11 and 13), how to clone additional sequences (e.g., *env* sequences) from patient isolates for use in preparation of additional constructs (see Example 15), how to test immunogenicity of the constructs (see Example 12), as well as how to conduct a vaccine trial to assess the efficacy of the constructs, (see Example 14). One of ordinary skill in the art, given these teachings of the Specification, would be able to generate constructs other than those specifically taught in the Specification for use in the methods of the invention.

Route of Administration

The Examiner stated that the route of administration is not limited to the route demonstrated by Applicants or known in the art to be effective for DNA vaccination. As indicated in the Specification (see, e.g., p. 9, lines 11-21), a wide variety of routes are suitable for DNA vaccination. The success of several routes can be seen, for example, in Example 4 (page 22, line 19 *et seq.*), where immunization by intramuscular, intravenous, and a combination of

routes (intramuscular, intravenous, and intraperitoneal) provided excellent protection after challenge with disease; immunization by intranasal (mucosal) route provided good protection after challenge with disease; and immunization by intradermal or subcutaneous routes provided protection after challenge with disease that was superior to the control immunizations. In addition, gene-gun delivered DNA to the epidermis provided excellent protection after challenge with disease (see Example 6, page 28, line 8 *et seq.*). Furthermore, similar results were obtained with gene gun immunization and multiple-route immunization in the simian trial described in the Declaration of Dr. Harriet Robinson. Thus, one of ordinary skill in the art would understand that a variety of routes of administration can be used for the methods of the invention.

Additional Antigens

The Examiner stated that Claim 67 required use of coding sequences of other antigens. In order to facilitate prosecution of the application, Claim 67 has been canceled.

Immunization and Protection Against Disease

The Examiner states that is was not clear whether any level of protection was realized in the Data Declaration. The Examiner further states that the Specification "implies that a therapeutic response, hence an improvement in the disease manifestation of the patient" is necessary. A "therapeutic response" resulting in an "improvement in disease manifestation" as stated by the Examiner implies a treatment for ameliorating disease after infection. However, the methods of the invention are not drawn to *treatment*, but rather, to immunizing which results in protection against disease.

The data described in the Data Declaration do demonstrate immunizing and protection against disease, as described in the Specification. As indicated above, "immunization" refers to production of an immune response which protects, *partially or totally*, from the *manifestations of infection* (i.e., disease) caused by the infectious agent, and can result in protection against infection, or infection to a lesser extent than would occur without immunization. Thus, "immunizing" includes generation of an immune response that *lessens or eliminates* manifestations of disease after infection with the infectious agent.

The experiments described in the Data Declaration relate to assessment of the ability of a nucleic acid vaccine to protect against disease in a highly virulent, uncloned SIVmac251 rhesus macaque model. The virus used generally causes ≥ 50% incidence of AIDS during the first year of infection (see, e.g., description of the virulence of the particular virus in Lu, S. *et al.*, "Simian Immunodeficiency Virus DNA Vaccine Trial in Macaques," *J. Virol. 70(6)*:3978-3991 (1996), a copy of which was submitted previously). In the case of highly virulent models, partial protection, rather than complete protection, against disease is usually expected.

As described in the Data Declaration, a more rapid reduction of viral loads to chronic levels was achieved in the immunized animals, in comparison to the rate of reduction in control animals. The ability of the vaccinations to effect such a rapid reduction of viral loads was particularly noteworthy in view of the virulence of the challenge virus. If a less virulent challenge virus were used, one could reasonably expect that even greater protection (e.g., further reduction of viral loads or other protective immune responses) could be achieved.

Rapid reduction of viral load is indicative of *a response which protects, at least partially, against manifestations of disease*, by attenuating the acute phase of infection. Thus, Applicants have demonstrated successful immunization, as it is described in the Specification.

Animal Model

The Examiner states that the references cited by Applicants (i.e., Gardner, M.B., *Antiviral. Res. 15*:267-286 (1991); Gardner, M.B., *Dev. Biol. Stand. 72*:259-266 (1990); Johnson, P.R. and Hirsch, V.M., *Int. Rev. Immunol. 8*:55-63 (1992); and McClure, H.M. *et al.*, *Ann. NY Acad. Sci. 616*:287-298 (1990)) with regard to the macaque model state only that the model is important for study of infection, and do not correlate to a model for determining vaccination strategies.

The references previously cited by Applicants were selected, in part, because they demonstrate the state of the art at the time the application was filed; they were further selected because of statements concerning the use of the models in development of vaccines. For example, the Gardner (1991) reference states:

> Animal lentivirus infections provide a valuable resource for understanding mechanisms of pathogenesis and for development of effective antiviral drugs and *vaccines* with direct relevance to HIV and AIDS (p. 268, Introduction, citations omitted and emphasis added).

This Gardner reference goes on to describe vaccine trials in the macaque model system (see page 269 *et seq.*). Thus, this Gardner reference clearly sets forth that animal lentivirus infections, such as SIV infection in macaques, are useful for development of vaccines, as exemplified by several studies using the SIV macaque model for vaccine trials.

As another example, the McClure reference states in its introduction:

> The magnitude and continuing growth of the current worldwide AIDS pandemic make the development of effective vaccines and antiviral drugs of utmost urgency. These efforts, especially studies of the pathogenesis of retroviral infections and testing of antiretroviral drugs, immune system modulators, and *vaccines* will be greatly facilitated by access to appropriate animal models. The SIV-infected nonhuman primate has been established as an excellent animal model system for conducting such studies. (p. 287, Introduction; citations omitted and emphasis added.)

Thus, the McClure reference specifically states that SIV-infected nonhuman primates are an excellent animal model system for studies which include studies of vaccines.

In view of these considerations, one of ordinary skill in the art, given the specification and the state of the art at the time the application was filed, as demonstrated by these references previously cited by Applicants, would find the macaque model described in the specification and used in the Data Declaration to be an appropriate model that would be predictive for HIV vaccination.

CONCLUSION

In view of the amendments and discussion presented above, the claims are in condition for allowance. Applicants' Attorney respectfully requests reconsideration and withdrawal of the remaining rejections.

If the Examiner believes that a telephone conversation would expedite prosecution of the application, the Examiner is invited to call Elizabeth W. Mata at (915) 845-3558. If Elizabeth W. Mata cannot be reached, the Examiner is invited to call David E. Brook at (781) 861-6240.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

David E. Brook, R.N. 22592

By for Elizabeth W. Mata

Elizabeth W. Mata
Registration No. 38,236
Telephone: (915) 845-3558
Facsimile: (915) 845-3237

Lexington, Massachusetts 02421-4799
Dated: 1/25/01